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EDITORIAL OFFICES

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42 Bedford Square,
London WC1B 3SL, UK
Telephone (+44) (0) 171 436 4981
Fax (+44) (0) 171 436 7550
(or 323 6441)

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WRITING FOR THE LANCET

Guidelines for authors are published
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Editor

A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)

CAPRIE Steering Committee*

Summary

Background Many clinical trials have evaluated the benefit of long-term use of antiplatelet drugs in reducing the risk of clinical thrombotic events. Aspirin and ticlopidine have been shown to be effective, but both have potentially serious adverse effects. Clopidogrel, a new thienopyridine derivative similar to ticlopidine, is an inhibitor of platelet aggregation induced by adenosine diphosphate.

Methods CAPRIE was a randomised, blinded, international trial designed to assess the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of a composite outcome cluster of ischaemic stroke, myocardial infarction, or vascular death; their relative safety was also assessed. The population studied comprised subgroups of patients with atherosclerotic vascular disease manifested as either recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease. Patients were followed for 1 to 3 years.

Findings 19 185 patients, with more than 6300 in each of the clinical subgroups, were recruited over 3 years, with a mean follow-up of 1.91 years. There were 1960 first events included in the outcome cluster on which an intention-to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischaemic stroke, myocardial infarction, or vascular death compared with 5.83% with aspirin. These rates reflect a statistically significant ($p=0.043$) relative-risk reduction of 8.7% in favour of clopidogrel (95% CI 0.3–16.5). Corresponding on-treatment analysis yielded a relative-risk reduction of 9.4%. There were no major differences in terms of safety. Reported adverse experiences in the clopidogrel and aspirin groups judged to be severe included rash (0.26% vs 0.10%), diarrhoea (0.23% vs 0.11%), upper gastrointestinal discomfort (0.97% vs 1.22%), intracranial haemorrhage (0.33% vs 0.47%), and gastrointestinal haemorrhage (0.52% vs 0.72%), respectively. There were ten (0.10%) patients in the clopidogrel group with significant reductions in neutrophils ($<1.2 \times 10^9/L$) and 16 (0.17%) in the aspirin group.

Interpretation Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death. The overall safety profile of clopidogrel is at least as good as that of medium-dose aspirin.

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*Study organisation given at end of paper

Correspondence to: Professor M Gent, Clinical Trials Methodology Group, Hamilton Civic Hospitals Research Centre, 711 Concession Street, Hamilton, Ontario, Canada L8V 1C3

Introduction

There have been several randomised trials of antiplatelet drugs in patients with disorders in which platelet activation is involved.¹ Their purpose was to determine the extent of reduction in various subsequent risks; in particular, risks of ischaemic stroke, myocardial infarction, and death from vascular disease (vascular death). Patients at increased risk of such outcomes included those with atherothrombotic disease such as transient ischaemic attacks or mild stroke, moderate or severe stroke, unstable angina, acute and remote myocardial infarction, and atherosclerotic peripheral arterial disease.^{2,3}

Interpretation of these studies has been inconsistent. Many investigators and practitioners apply the results from a particular subgroup of patients, such as those with transient ischaemic attacks or mild stroke, only to patients with that disorder and not to patients with different atherothrombotic manifestations, although it is both clinically and biologically plausible to assume that similar treatment benefits would extend to them. There is evidence from the Antiplatelet Trialists' Collaboration to support a widespread effect.^{2,3} A meta-analysis of 142 trials, including more than 73 000 high-risk patients in various disease categories, shows clearly that antiplatelet drugs reduce the incidence of a composite outcome of ischaemic stroke, myocardial infarction, and vascular death, the relative-odds reduction being 27%, which is consistent over a wide range of clinical manifestations as well as across subgroups of patients at varying risks within specific clinical subgroups.

Both aspirin^{1,4} and ticlopidine^{5,6} have been shown to be of benefit in placebo-controlled studies. Relative-risk reductions for the composite outcomes of stroke, myocardial infarction, or vascular death were 25% with aspirin and 33% with ticlopidine. In three studies in which aspirin was compared with ticlopidine, the odds reduction, while not statistically significant, favoured ticlopidine by 10%.⁷ However, both drugs have potentially serious adverse effects: gastrointestinal discomfort and bleeding with aspirin;⁴ and bone-marrow depression, rash, and diarrhoea with ticlopidine.⁶

Clopidogrel (Plavix) is a new thienopyridine derivative, chemically related to ticlopidine (figure 1). Its activity in animal models of thrombosis is greater than that of ticlopidine.⁷ Clopidogrel prevents arterial as well as venous thrombosis and reduces atherogenesis in several animal species.^{7,8} Clopidogrel blocks activation of platelets by adenosine diphosphate (ADP) by selectively and irreversibly inhibiting the binding of this agonist to its receptor on platelets, thereby affecting ADP-dependent activation of the GpIIb-IIIa complex, the major receptor for fibrinogen present on the platelet surface.^{9,10} In platelet-aggregation studies, clopidogrel, 75 mg once daily, produces inhibition of ADP-induced platelet

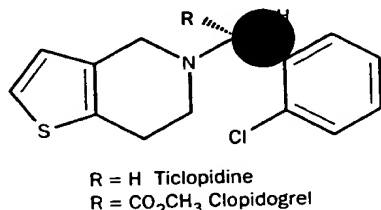


Figure 1: Structure of clopidogrel and ticlopidine
Clopidogrel is the (S) active enantiomer of a racemate.

aggregation equivalent to that of ticlopidine, 250 mg twice daily.

CAPRIE was a randomised clinical trial to assess the potential benefit of clopidogrel, compared with aspirin, in reducing the risk of ischaemic stroke, myocardial infarction, or vascular death in patients with recent ischaemic stroke, recent myocardial infarction, or peripheral arterial disease.

Methods

Protocol

Patient eligibility Clinical evaluation had to establish the diagnosis of ischaemic stroke, myocardial infarction, or symptomatic atherosclerotic peripheral arterial disease. Inclusion and exclusion criteria are shown in tables 1 and 2. Eligible patients who gave informed consent were entered into the study. Use of anticoagulants or antiplatelet drugs was discontinued before randomisation and thrombolytic treatment should not have been received within the previous 48 h. The study protocol was reviewed and approved by the institutional review board or ethics committee of each of the participating centres.

Treatment and follow-up Patients received blister packs containing either 75 mg tablets of clopidogrel plus aspirin placebo or 325 mg tablets of aspirin plus clopidogrel placebo. Patients were asked to take one of each tablet daily with their morning meal. We planned to recruit patients over 3 years with a further year of follow-up and that patients would receive study drugs for a maximum of 3 years and a minimum of 1 year.

Baseline assessment recorded demographic information, the qualifying event or condition, medical history, general physical examination, and concomitant medications. Except in the early stages of the study, follow-up visits took place monthly for the first 4 months and every 4 months thereafter. At these visits, information was collected on adverse events and use of study drug and concomitant medications, and blood was taken for haematological and biochemical assessments by one of three central laboratories. Platelet aggregation testing was forbidden since the results might have revealed treatment allocation. Compliance with study drug was assessed by counting of returned tablets at follow-up visits. Patients were provided with a list of common over-the-counter aspirin-containing products and were instructed to avoid them.

Human safety data on clopidogrel were limited at the start of CAPRIE, so the initial follow-up schedule had weekly assessments of blood counts and 2-weekly assessments of biochemistry during the first 3 months. After 500 patients had been entered, a blinded review of these data by the Steering Committee did not show any cause for concern, so the frequency of these assessments was halved. After data had been collected on the first 1000 patients followed for 3 months, the Steering Committee received a report on these laboratory results prepared by the External Safety and Efficacy Monitoring Committee, classified by treatment A or B, on the basis of which the follow-up schedule was relaxed to that stated above.

Alert values of less than $1.2 \times 10^9/L$ for neutrophils and less than $100 \times 10^9/L$ for platelets were established, whereby investigators were to begin daily complete blood counts. Should the corresponding counts fall below $0.45 \times 10^9/L$ or $80 \times 10^9/L$,

Ischaemic stroke
(including retinal
and lacunar infarction)

Focal neurological deficit likely to be of atherothrombotic origin
Onset ≤ 1 week and ≤ 6 months before randomisation
Neurological signs persisting ≥ 1 week from stroke onset
CT or MRI ruling out haemorrhage or non-relevant disease

Myocardial infarction

Onset ≤ 35 days before randomisation
Two of:
Characteristic ischaemic pain for ≥ 20 min
Elevation of CK, CK-MB, LDH, or AST to $2 \times$ upper limit of laboratory normal with no other explanation
Development of new ≥ 40 Q waves in at least two adjacent ECG leads or new dominant R wave in V1 ($R \geq 1$ mm $>$ S in V1)

**Atherosclerotic peripheral
arterial disease**

Intermittent claudication (WHO: leg pain on walking, disappearing in <10 min on standing) of presumed atherosclerotic origin; and ankle/arm systolic BP ratio ≤ 0.85 in either leg at rest (two assessments on separate days); or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty with no persisting complications from intervention

CT=computed tomography; MRI=magnetic resonance imaging; CK=creatinine kinase;
LDH=lactate dehydrogenase; AST=aspartate aminotransferase;
ECG=electrocardiogram; BP=blood pressure; WHO=World Health Organization.

Table 1: Inclusion criteria

respectively, the study drug was to be permanently discontinued. Near the end of the study, all patients for whom a decrease to below the alert value had been reported were reviewed, blind to treatment allocation, by a haematologist to rule out laboratory errors, spoiled samples, and random fluctuations around an inherently low baseline.

Adverse experiences of patients were recorded for the duration of their follow-up, except in those patients who permanently discontinued study drug early; for these patients adverse experiences were counted up to 28 days after discontinuation.

Outcome events Non-fatal events were ischaemic stroke, myocardial infarction, primary intracranial haemorrhage, and leg amputation (table 3). Deaths were classified as due to ischaemic stroke, myocardial infarction, haemorrhage, other vascular causes, or non-vascular causes. The classification of fatal ischaemic stroke or myocardial infarction was based on either death within 28 days after the onset of signs or symptoms of the acute outcome event, in the absence of other clear causes, or on necropsy findings. Other vascular deaths were any deaths that were not clearly non-vascular and did not meet the criteria for fatal stroke, fatal myocardial infarction, or haemorrhage. Deaths considered by the Central Validation Committee to be directly related to the qualifying event were classified as other vascular.

Sample size We planned to recruit 15 000 patients, 5000 in each of the clinical subgroups, over 3 years and to terminate the study

Age <21 years

Severe cerebral deficit likely to lead to patient being bedridden or demented

Carotid endarterectomy after qualifying stroke

Qualifying stroke induced by carotid endarterectomy or angiography

Patient unlikely to be discharged alive after qualifying event

Severe co-morbidity likely to limit patient's life expectancy to less than 3 y

Uncontrolled hypertension

Scheduled for major surgery

Contraindications to study drugs:

Severe renal or hepatic insufficiency

Haemostatic disorder or systemic bleeding

History of haemostatic disorder or systemic bleeding

History of thrombocytopenia or neutropenia

History of drug-induced haematologic or hepatic abnormalities

Known to have abnormal WBC, differential, or platelet count

Anticipated requirement for long-term anticoagulants, non-study antiplatelet drugs

or NSAIDs affecting platelet function

History of aspirin sensitivity

Women of childbearing age not using reliable contraception

Currently receiving investigation drug

Previously entered in other clopidogrel studies

Geographic or other factors making study participation impractical

WBC=white blood count; NSAIDs=non-steroidal anti-inflammatory drugs

Table 2: Exclusion criteria

| | |
|---|---|
| Ischaemic stroke | Acute neurological vascular event with focal signs for ≥ 24 h. If in a new event, without evidence of intracranial haemorrhage. If worsening of previous event, must have lasted >1 week, or more than 24 h if accompanied by appropriate CT or MRI findings |
| Myocardial infarction | As for inclusion criteria (see table 1) |
| Primary intracranial haemorrhage | Intracerebral haemorrhage (including intracranial and subarachnoid), and subdural haematoma documented by appropriate neuroimaging investigations. (Traumatic intracranial haemorrhage was recorded but not counted as outcome event) |
| Leg amputation | Only if above the ankle and not done for trauma or cancer. (subsequent amputations of a given leg were not counted as outcome events) |

For abbreviations, see table 1.

Table 3: Non-fatal outcome events

after 1 further year of follow-up. If recruitment over time was uniform, this sample would have resulted in a mean duration of potential follow-up of 2.33 years per patient and 35 000 patient-years at risk. We assumed expected 3-year event rates would be 25% for the primary outcome cluster for patients entering the study with recent stroke or myocardial infarction and 14% for patients entering with peripheral arterial disease. With a two-sided $\alpha=0.05$, the study was expected to have 90% power to detect an overall relative-risk reduction of 11.6%, based on an intention-to-treat analysis. If this were the true effect, the expected width of the corresponding 95% CI would be about 8%.

Patient recruitment was achieved well ahead of schedule and 15 000 patients had been randomised after only 2 years and 3 months. To stop recruitment at that time and close the study after 1 further year of follow-up would have resulted in less than 35 000 potential patient-years at risk. A blinded review of overall outcome event rates showed them to be lower than initial expectations. The Steering Committee decided to continue patient recruitment but to stagger recruitment closing dates and, hence, completion dates, 1 year later: recruitment of patients with peripheral arterial disease would finish 2 months before patients with myocardial infarction who would finish 2 months before patients with stroke. The plan was expected to produce similar numbers of more than 6000 in each of the clinical subgroups and facilitate study closedown. A revised total of 40 000 potential patient-years at risk was expected and the revised estimate of relative-risk reduction that could be detected with 90% power would be 12–13%.

Primary analysis of efficacy was based on the first occurrence of an event in the outcome cluster of ischaemic stroke, myocardial infarction, or vascular death. A secondary outcome cluster included amputation and a further comparison was based on vascular death only. Although the main focus was on events presumed to be due to atherosclerotic disease, primary intracranial haemorrhage and fatal bleeds were possible adverse events, so these were included in an assessment of overall net benefit with the outcome cluster of any stroke, myocardial infarction, or death from any cause. A fourth secondary analysis assessed all-cause mortality.

Assessments of relative efficacy were based on a comparison between the two treatment groups of the cumulative risk over time of each of the five prespecified outcomes. Survival curves based on the proportion of patients remaining event-free were estimated by the Kaplan-Meier method¹¹ and compared by a two-sided Mantel-Haenszel test,^{12,13} stratified by clinical subgroup.

Two analytical strategies were planned: an intention-to-treat analysis in which all patients randomised were considered at risk to their planned end of study, irrespective of their compliance with study protocol, and an on-treatment analysis in which a patient's time at risk was censored 28 days after early permanent discontinuation of study drug. In addition, to take into account any imbalances between the two treatment groups in baseline prognostic variables, analyses were repeated with adjustment procedures based on Cox's proportional hazards model.¹⁴

Primary analysis, however, was to be the unadjusted intention-to-treat comparison based on the outcome cluster of ischaemic stroke, myocardial infarction, or vascular death. Similar analyses were carried out for each of the clinical subgroups.

Safety assessments were based on the proportion of patients experiencing one or more episodes of a specific adverse event. Such proportions in the two treatment groups were compared by χ^2 test.

Patients lost to follow-up In May, 1996 (3 months after the end of the trial) a search agency was contracted by the Coordinating and Methods Centre to help trace patients who were lost to follow-up.

Study organisation

The study involved 384 clinical centres from 16 countries and followed US Investigational New Drug regulations and European Good Clinical Practice guidelines, as well as local requirements. In order to make the most of expertise and resources of both researchers and the industrial backers of the trial, a complex organisation was created.

The *Steering Committee*, comprising university-based and industry-based scientists, had overall responsibility for the design, execution, analysis, and reporting of the study. This committee met every 6 months to address policy issues and to monitor study execution and management. The Steering Committee has responsibility for all publications resulting from the study.

The *Central Validation Committee* was responsible for validating all reported non-fatal outcome events and reported classifications of cause of death, with a secretariat at the *Coordinating and Methods Centre* in Hamilton, Ontario. After an outcome event dossier was received, only the secretariat had any communication with the reporting investigator about the validation of the event. The secretariat maintained a database of validated outcome events, a copy of which was not provided to the industrial backers before the end of the study.

Each reported outcome event was reviewed independently by two members of the Central Validation Committee. Any disagreements between them were resolved by committee review. Committee disagreement with a reported outcome event was made known to the investigator who could either agree with the Committee or provide additional information to support the initial judgment. When agreement could still not be reached, the decision of the Central Validation Committee was final.

The *External Safety and Efficacy Monitoring Committee* had responsibility for monitoring of patient safety and for formal interim analyses of efficacy. This committee had an associated *Independent Statistical Centre* in Lyon, France, that received an updated copy of the study database every 3 months from the Coordinating and Methods Centre. Information on study-drug allocation was merged with study data and routine aggregate safety summaries produced. In addition to safety monitoring, there were to be three interim analyses of efficacy, based on the primary outcome cluster, when 25%, 50%, and 75% of the planned patient-years at risk had accumulated. Stopping guidelines used a Peto-Haybittle type rule based on the p value of the Mantel-Haenszel test. A two-sided type I error of 0.001 was used which preserved a type I error of 0.048 for the end-of-study analysis. The results of interim analyses were to be disclosed to the Chairman of the Steering Committee only if the stopping rule was met. The quarterly External Safety and Efficacy Monitoring Committee reports also included a futility stopping rule based on the current 95% CI on the relative-risk reduction for the primary outcome cluster; the upper end of the interval had to exceed a 14% relative-risk reduction in favour of clopidogrel compared with aspirin, otherwise the Steering Committee had to be informed. After each quarterly review, a report was sent to the chairman of the Steering Committee stating only that there was no reason not to continue the trial as planned.

The *Coordinating and Methods Centre* at Hamilton facilitated and oversaw the study and provided methodological and administrative support to all committees, investigators, and other study personnel.

| Characteristic | All patients | | Stroke subgroup | | MI subgroup | | PAD subgroup | |
|---|-------------------------|---------------------|-------------------------|---------------------|-------------------------|---------------------|-------------------------|---------------------|
| | Clopidogrel (n=9599) | Aspirin (n=9586) | Clopidogrel (n=3233) | Aspirin (n=3198) | Clopidogrel (n=3143) | Aspirin (n=3159) | Clopidogrel (n=3223) | Aspirin (n=3229) |
| Mean (SD) age in years | 62.5 (11.1) | 62.5 (11.1) | 64.5 (11.2) | 64.7 (11.0) | 58.6 (11.4) | 58.3 (11.3) | 64.2 (9.6) | 64.4 (9.7) |
| % male | 72 | 72 | 64 | 63 | 81 | 81 | 73 | 72 |
| % white | 95 | 95 | 91 | 91 | 96 | 98 | 98 | 98 |
| Percentage of patients with a history of: | | | | | | | | |
| Ischaemic stroke* | 9 | 9 | 17 | 19 | 2 | 2 | 6 | 6 |
| TIA/RIND | 10 | 10 | 19 | 19 | 3 | 2 | 8 | 8 |
| Diabetes mellitus | 20 | 20 | 25 | 26 | 14 | 15 | 21 | 21 |
| Hypertension | 52 | 51 | 65 | 65 | 39 | 38 | 51 | 51 |
| Hypercholesterolaemia | 41 | 41 | 37 | 38 | 41 | 42 | 45 | 45 |
| Angina (stable) | 22 | 22 | 14 | 14 | 25 | 25 | 26 | 27 |
| Angina (unstable) | 9 | 9 | 3 | 3 | 17 | 17 | 6 | 6 |
| Myocardial infarction* | 17 | 16 | 13 | 11 | 17 | 17 | 21 | 21 |
| Congestive heart failure | 6 | 5 | 4 | 4 | 7 | 7 | 6 | 6 |
| Cardiomegaly | 5 | 4 | 6 | 5 | 4 | 3 | 4 | 4 |
| Atrial fibrillation | 4 | 4 | 4 | 4 | 5 | 5 | 4 | 4 |
| Intermittent claudication* | 5 | 4 | 8 | 8 | 6 | 5 | .. | .. |
| Current cigarette smoker | 29 | 30 | 22 | 22 | 28 | 29 | 38 | 38 |
| Ex cigarette smoker | 49 | 49 | 43 | 44 | 51 | 50 | 53 | 52 |

*Not including the qualifying event; MI=myocardial infarction; PAD=peripheral arterial disease; TIA=transient ischaemic attack; RIND=reversible ischaemic neurological deficit.

Table 4: Baseline characteristics

Regional Data Collection Centres were at Hamilton, responsible for all the Canadian centres, and in affiliates of industrial backers—one in the USA and two in Europe.

Assignment

The Independent Statistical Centre provided computer-generated balanced blocks of four treatments with random allocation to clopidogrel or aspirin, stratified by clinical centre and the three disease subgroups. Access to this code was restricted to the Independent Statistical Centre, the Chairman of the External Safety and Efficacy Monitoring Committee, and to two independent companies responsible for preparing the study drugs. A copy of the randomisation scheme was deposited with a public notary.

Blinding

Patients were allocated study drugs sequentially from supplies at the clinical centre packaged in a predetermined order in a carton that contained supplies for four patients. These supplies were in the form of blister packs containing either 75 mg tablets of clopidogrel plus aspirin placebo tablets or 325 mg aspirin tablets plus clopidogrel placebo tablets, such blister packs being indistinguishable from one another. The initial supply of study drug had a sealed treatment code label attached which once opened could not be resealed in its original form; this was retained at the clinical centre for emergency code-breaking purposes. There were 21 (0.11%) code breaks during the course of the study, of which 11 were patients in the clopidogrel group and ten in the aspirin group. At the close of the study, a

representative sample of 3358 code-break labels were retrieved and the Independent Statistical Centre verified that there were no code-break labels opened other than those previously reported to them.

Analysis

At the end of the study, the Coordinating and Methods Centre provided a copy of the final study database to the Independent Statistical Centre which, in turn, provided a copy of the randomisation code to the Coordinating and Methods Centre. The Independent Statistical Centre then carried out the primary analysis and four secondary analyses to verify the corresponding analyses conducted by the Coordinating and Methods Centre. A copy of the randomisation scheme was not provided to the industrial backers until after the Steering Committee had met to be appraised of the findings from the study.

| Event type | Clopidogrel | Aspirin | Total |
|----------------------------|-------------|-------------|-------------|
| Non-fatal events | | | |
| Non-fatal ischaemic stroke | 472 | 504 | 976 |
| Non-fatal MI | 255 | 301 | 556 |
| Non-fatal primary ICH | 14 | 24 | 38 |
| Amputation | 52 | 47 | 99 |
| Fatal events | | | |
| Fatal ischaemic stroke | 37 | 42 | 79 |
| Fatal MI | 53 | 75 | 128 |
| Haemorrhagic death | 23 | 27 | 50 |
| Other vascular death | 260 | 261 | 521 |
| Non-vascular death | 187 | 166 | 353 |
| Total | 1353 | 1447 | 2800 |

MI=myocardial infarction; ICH=intracranial haemorrhage.

Table 5: Validated events

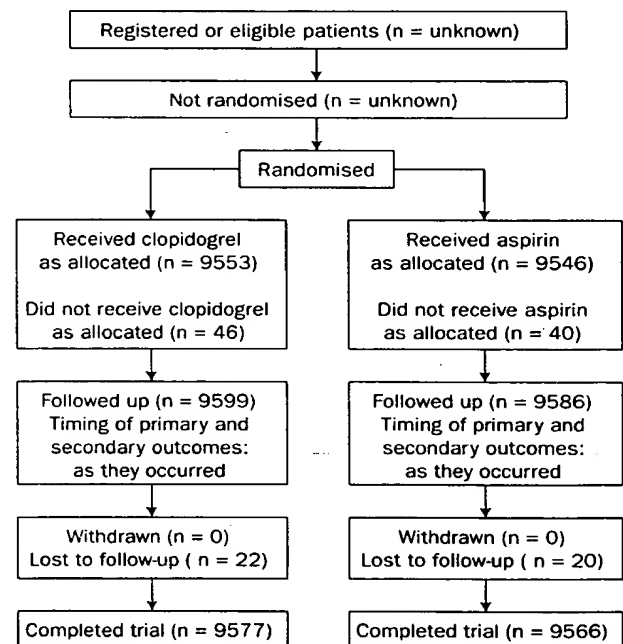


Figure 2: Participant progress through trial

| Outcome event cluster and treatment group | First outcome events | | | Event rate (%) | Relative-risk reduction (95% CI) | p |
|--|----------------------|-------|-------|----------------|----------------------------------|-------|
| | Non-fatal | Fatal | Total | | | |
| Ischaemic stroke, MI, or vascular death (primary cluster) | | | | | | |
| Clopidogrel (n=17636*) | 631 | 308 | 939 | 5.32% | 8.7% (0.3 to 16.5) | 0.043 |
| Aspirin (n=17519) | 700 | 321 | 1021 | 5.83% | | |
| Ischaemic stroke, MI, amputation, or vascular death | | | | | | |
| Clopidogrel (n=17594) | 677 | 302 | 979 | 5.56% | 7.6% (-0.8 to 15.3) | 0.076 |
| Aspirin (n=17482) | 737 | 314 | 1051 | 6.01% | | |
| Vascular death | | | | | | |
| Clopidogrel (n=17482) | .. | 350 | 350 | 1.90% | 7.6% (-6.9 to 20.1) | 0.29 |
| Aspirin (n=18354) | .. | 378 | 378 | 2.06% | | |
| Any† stroke, MI, or death from any cause | | | | | | |
| Clopidogrel (n=17622) | 643 | 490 | 1133 | 6.43% | 7.0% (-0.9 to 14.2) | 0.081 |
| Aspirin (n=17501) | 720 | 487 | 1207 | 6.90% | | |
| Death from any cause | | | | | | |
| Clopidogrel (n=18377) | .. | 560 | 560 | 3.05% | 2.2% (-9.9 to 12.9) | 0.71 |
| Aspirin (n=18354) | .. | 571 | 571 | 3.11% | | |

*Patient-years at risk for outcome cluster; †includes primary intracranial hemorrhage; MI=myocardial infarction.

Table 6: Intention-to-treat analysis—primary and secondary outcome clusters

Results

Participants and follow-up

19 185 patients from 384 clinical centres were randomised between March, 1992, and February, 1995. Patient follow-up was completed by February, 1996, resulting in 36 731 patient-years at risk. Mean duration of follow-up was 1.91 years.

During the study, 42 patients (0.22%) were lost to follow-up, 22 in the clopidogrel group and 20 in the aspirin group (figure 2); the resulting loss in total patient-years at risk was 49 (0.13%). These 42 patients were included in the analyses with their follow-up censored at the time of last contact.

4059 patients (21.2%) had study drug permanently discontinued early, for reasons other than the occurrence of an outcome event; 21.3% in the clopidogrel and 21.1% in the aspirin group. Reasons for stopping study drug early were similar in the two groups: adverse events (11.4%); withdrawn consent (4.7%); contraindicated medications (2.4%); non-compliance (1.8%); and other (0.8%). Mean follow-up while on study drug was 1.63 years for each treatment group.

With exclusion of follow-up after any early permanent discontinuation of study drug, mean compliance with clopidogrel and aspirin was similar at 91%. 46 patients in the clopidogrel group and 40 in the aspirin group never took any study drug.

Analysis

Baseline characteristics of randomised patients are shown in table 4. The treatment groups were well matched with respect to age, sex, race, and cardiovascular risk factors. After randomisation, 16 patients, ten in the clopidogrel group and six in the aspirin group, were found not to have the qualifying disease; most were entered as having ischaemic stroke but were subsequently found to be misdiagnosed, (eg, as multiple sclerosis or primary intracranial haemorrhage). The study drug was terminated within 4 months of randomisation for 13 of these patients but the other three patients were continued on study drug; all 16 continued to be followed as per protocol and included in the analyses.

There were 2800 validated outcome events, of which 1669 were non-fatal and 1131 were fatal (table 5). There were 1171 patients in the clopidogrel group and 1236 patients in the aspirin group who had an outcome event of

whom 158 and 182, respectively, had more than one event.

The primary analysis of efficacy was by intention-to-treat and based on the incidence of the first occurrence of ischaemic stroke, myocardial infarction, or vascular death among all patients randomised. There were 939 events in the clopidogrel group during 17 636 patient-years at risk, an average rate per year of 5.32%. There were 1021 events in the aspirin group during 17 519 patient-years at risk, an average rate per year of 5.83%. Relative-risk reduction, estimated from a Cox proportional-hazard model, was 8.7% (95% CI 0.3–16.5) in favour of clopidogrel ($p=0.043$, table 6). The cumulative proportions of patients who experienced an event in this primary outcome cluster over 3 years are shown in figure 3.

Results of the analyses of the four predefined secondary outcome clusters are also shown in table 6. The estimated relative-risk reductions with clopidogrel were consistently 7% to 8% when the outcomes were predominantly vascular events but the relative-risk reduction was smaller for all-cause mortality, of which 36% was non-vascular.

Estimated treatment effects for both the primary and secondary outcome clusters remained virtually unchanged when adjusted for relevant prognostic baseline variables.

Main baseline characteristics for each of the subgroups are shown in table 4. Patients in the ischaemic stroke and peripheral arterial disease groups were similar in age and 6

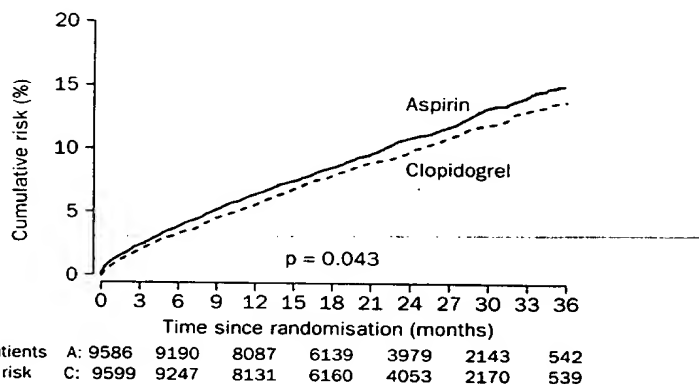


Figure 3: Cumulative risk of Ischaemic stroke, myocardial infarction, or vascular death
A=aspirin; C=clopidogrel.

| Subgroup and treatment group | Individual first outcome events | | | | Other vascular death | Total | Event rate per year | Relative-risk reduction (95% CI) | p |
|------------------------------|---------------------------------|-------|-----------|-------|----------------------|-------|---------------------|----------------------------------|--------|
| | Stroke | | MI | | | | | | |
| | Non-fatal | Fatal | Non-fatal | Fatal | | | | | |
| Stroke | | | | | | | | | |
| Clopidogrel (nyrs=6054*) | 298 | 17 | 33 | 11 | 74 | 433 | 7.15% | 7.3% (-5.7 to 18.7) | 0.26 |
| Aspirin (nyrs=5979) | 322 | 16 | 37 | 14 | 72 | 461 | 7.71% | | |
| MI | | | | | | | | | |
| Clopidogrel (nyrs=5787) | 37 | 5 | 143 | 20 | 86 | 291 | 5.03% | -3.7% (-22.1 to 12.0) | 0.66 |
| Aspirin (nyrs=5843) | 34 | 8 | 152 | 22 | 67 | 283 | 4.84% | | |
| PAD | | | | | | | | | |
| Clopidogrel (nyrs=5795) | 70 | 11 | 50 | 18 | 66 | 215 | 3.71% | 23.8% (8.9 to 36.2) | 0.0028 |
| Aspirin (nyrs=5797) | 74 | 8 | 81 | 27 | 87 | 277 | 4.86% | | |
| All patients | | | | | | | | | |
| Clopidogrel (nyrs=17636) | 405 | 33 | 226 | 49 | 226 | 939 | 5.32% | 8.7% (0.3 to 16.5) | 0.043 |
| Aspirin (nyrs=17519) | 430 | 32 | 270 | 63 | 226 | 1021 | 5.83% | | |

*Patient years at risk. MI=myocardial infarction; PAD=peripheral arterial disease.

Table 7: Treatment effect by subgroup—*ischaemic stroke, MI, or vascular death*

years older on average than those in the myocardial infarction group, and there were differences in the proportion of men across the three clinical subgroups. Previous history of vascular events and vascular risk factors show that there was an overlap in the three clinical subgroups. For example, 12% of the stroke subgroup and 8% peripheral arterial disease reported a history of myocardial infarction. 2% of the younger myocardial infarction subgroup reported previous stroke and 6% peripheral arterial disease. 6% of the peripheral arterial disease group had experienced a previous stroke and 21% a previous myocardial infarction. About 18% of the stroke subgroup had experienced at least one additional stroke before their qualifying event; similarly the qualifying myocardial infarction was not their first for 17% of the myocardial infarction subgroup. 50% of the study cohort had a history of hypertension, 25% had a history of angina, and 20% had diabetes mellitus.

For the ischaemic stroke group, mean time from stroke onset to randomisation was 53 days; 59% of qualifying events were atherothrombotic and 40% lacunar. For the myocardial infarction group, mean time from onset of symptoms to randomisation was 17.6 days, 34% of the qualifying events were anterior and 57% were inferior. For the peripheral arterial disease group, mean duration of symptomatic disease before randomisation was 4.2 years and 63% were eligible on the basis of arterial intervention. For those qualifying on the basis of current claudication, the mean ankle/arm blood pressure ratio at entry was 0.57. These baseline characteristics were similar between the two treatment groups.

Analyses based on the primary outcome cluster of ischaemic stroke, myocardial infarction, or vascular death are summarised for each of the clinical subgroups in table 7, which also shows the type of first outcome event. Within this primary cluster of ischaemic events, recurrent stroke and stroke deaths were most common within the stroke subgroup and fatal or non-fatal myocardial infarctions most common in the myocardial infarction subgroup. Patients with peripheral arterial disease had approximately equal risks of stroke and myocardial infarction.

For patients with stroke, the average event rate per year in the clopidogrel group was 7.15% compared with 7.71% in the aspirin group, a relative-risk reduction of 7.3% (-5.7 to 18.7) in favour of clopidogrel ($p=0.26$). For patients with myocardial infarction, the average event rate per year was 5.03% in the clopidogrel group compared with 4.84% in the aspirin group; a relative-risk increase of 3.7% (22.1 to -12.0) associated with clopidogrel ($p=0.66$). For patients with peripheral arterial disease, the average event rate per year in the clopidogrel group was 3.71% compared with 4.86% in the aspirin group; a relative-risk reduction of 23.8% (8.9 to 36.2) in favour of clopidogrel ($p=0.0028$) (figure 4).

A test of heterogeneity of these three treatment effects, was statistically significant ($p=0.042$), suggesting that the true benefit may not be identical across the three clinical subgroups.

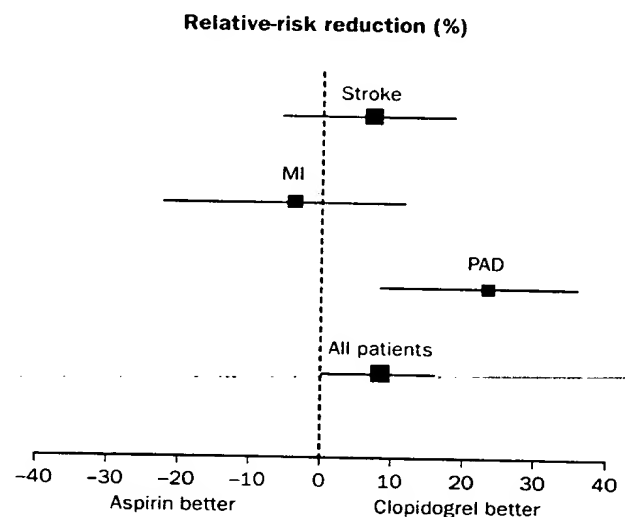


Figure 4: Relative-risk reduction and 95% CI by disease subgroup

MI=myocardial infarction; PAD=peripheral arterial disease.

| Patient and treatment subgroup | Ischaemic stroke, MI, vascular death | | Relative-risk reduction (95% CI) |
|--|--------------------------------------|---------|----------------------------------|
| | Events | Rate/yr | |
| PAD/stroke with previous MI (n=2144*) | | | |
| Clopidogrel (n=1963†) | 164 | 8.35% | 22.7% (4.9 to 37.2) |
| Aspirin (n=1825) | 196 | 10.74% | |
| Any previous MI (n=8446) | | | |
| Clopidogrel (n=7751) | 455 | 5.87% | 7.4% (-5.2 to 18.6) |
| Aspirin (n=7668) | 479 | 6.25% | |

PAD=peripheral arterial disease; MI=myocardial infarction; *Number of patients; †Number of patient years at risk

Table 8: Treatment effects of patients with a history of MI

Corresponding estimates of treatment effects based on the on-treatment analysis (while on study drug or within 28 days of early permanent discontinuation) were also made. Most of the on-treatment analyses yielded slightly increased treatment effects. In particular, the relative-risk reduction of 8.7% on the primary outcome cluster increased to 9.4% in on-treatment analysis.

The lack of observed benefit of clopidogrel over aspirin in the myocardial infarction subgroup and the evidence of possible heterogeneity of treatment effect among the clinical subgroups prompted a single additional analysis.

There were 2144 patients in the ischaemic stroke and peripheral arterial disease groups with a previous history of myocardial infarction. For the primary outcome cluster of ischaemic stroke, myocardial infarction, or vascular death, the average event rate per year in the clopidogrel group was 8.35% compared with 10.74% in the aspirin group, a relative-risk reduction of 22.7% (4.9-37.3) in favour of clopidogrel (table 8). When this group with a history of myocardial infarction is combined with the myocardial infarction (qualifying event) subgroup, the overall relative-risk reduction in favour of clopidogrel becomes 7.4% (-5.2 to 18.6).

There was no evidence of any unusual findings of adverse effects in either treatment group. Table 9 shows the proportion of patients ever reporting adverse experiences, those judged by the investigator to be clinically severe, and those which were sufficient to result in early permanent discontinuation of study drug. Liver function was monitored routinely, given the experimental stage of clopidogrel; no treatment-related effect was seen. The frequency of severe rash was higher with clopidogrel than with aspirin ($p=0.017$) as was the frequency of severe diarrhoea ($p=0.080$). More frequent with aspirin were severe upper gastrointestinal discomfort ($p=0.096$), intracranial haemorrhage ($p=0.23$), and gastrointestinal haemorrhage ($p=0.05$). There were also more patients with validated non-fatal primary intracranial haemorrhage or haemorrhagic death in the aspirin group, (51 [0.53%] vs 37 [0.39%]). There were no clinically significant

changes over time in the various laboratory measures, in particular for plasma cholesterol concentrations.

The independent blinded haematological review found the number of cases below the platelet-alert value was 25 (0.26%) in the clopidogrel group and 25 (0.26%) in the aspirin group; the numbers for low neutrophil counts were ten (0.10%) and 16 (0.17%). Among these latter cases, the neutrophil count fell below $0.45 \times 10^9/L$ for five (0.05%) and four (0.04%) patients in the clopidogrel and aspirin groups, respectively.

Discussion

CAPRIE is the first study of an antiplatelet drug to include patients from the clinical subgroups of ischaemic cerebrovascular, cardiac, and peripheral arterial disease under a common protocol. We reasoned from available evidence that in a study on prevention, separations within and amongst clinical subgroups are not necessary because the underlying condition is atherothrombosis which can become clinically manifest in different ways. This approach can be justified by the common aetiology because many patients have experienced one manifestation when they present to medical attention with another; because of the consistency of the effect of antiplatelet drugs across clinical subgroups; and because in necropsy studies, many patients who have atherosclerosis in one part of the body are found to have it in others.

CAPRIE was powered to detect a realistic treatment effect in the whole study cohort but not in each of the three clinical subgroups. The intention-to-treat analysis of the primary outcome cluster showed an overall relative-risk reduction of 8.7% ($p=0.043$), with 95% CI of 0.3-16.5. When the corresponding subgroup analyses were carried out separately for the ischaemic stroke, myocardial infarction, and peripheral arterial disease subgroups, the estimated relative-risk reductions were 7.3%, -3.7%, and 23.8%, respectively. A test for heterogeneity was significant ($p=0.042$) suggesting that the observed differences in these relative treatment effects were greater than might be due to chance. From these observed treatment effects, the possibility cannot be ruled out entirely that clopidogrel and aspirin are only equivalent in benefit in patients presenting with myocardial infarction or that the benefit of clopidogrel over aspirin is truly much greater in patients with peripheral arterial disease.

To help interpret the apparently discrepant finding in the myocardial infarction subgroup, an additional analysis, not specified in the protocol, was considered relevant because aspirin has similar benefits in preventing major ischaemic events in patients with acute myocardial infarction and in those with a remote history of myocardial infarction.³ There were 2144 patients in the stroke and peripheral arterial disease groups who had a distant past

| Adverse experience | Patients ever reporting | | Severe | | Study drug permanently discontinued | |
|------------------------------|-------------------------|----------------|-------------|-------------|-------------------------------------|--------------|
| | Clopidogrel | Aspirin | Clopidogrel | Aspirin | Clopidogrel | Aspirin |
| Rash | 578 (6.02%) | 442 (4.61%)* | 25 (0.26%) | 10 (0.10%)* | 86 (0.90%) | 39 (0.41%)* |
| Diarrhoea | 428 (4.46%) | 322 (3.36%)* | 22 (0.23%) | 11 (0.11%) | 40 (0.42%) | 26 (0.27%)* |
| Indigestion/nausea/vomiting | 1441 (15.01%) | 1686 (17.59%)* | 93 (0.97%) | 118 (1.23%) | 182 (1.90%) | 231 (2.41%)* |
| Any bleeding disorder | 890 (9.27%) | 890 (9.28%) | 132 (1.38%) | 149 (1.55%) | 115 (1.20%) | 131 (1.37%) |
| Intracranial haemorrhage | 34 (0.35%) | 47 (0.49%) | 30 (0.31%) | 41 (0.43%) | 20 (0.21%) | 32 (0.33%) |
| Gastrointestinal haemorrhage | 191 (1.99%) | 255 (2.66%)* | 47 (0.49%) | 68 (0.71%)* | 50 (0.52%) | 89 (0.93%)* |
| Abnormal liver function | 285 (2.97%) | 302 (3.15%)* | 11 (0.11%) | 9 (0.09%) | 22 (0.23%) | 28 (0.29%) |

*Statistically significant, $p<0.05$.

Table 9: Adverse experiences (number and percentage of patients)

history of myocardial infarction. When this cohort was combined with the 6302 patients who presented with myocardial infarction as the qualifying event, the overall relative-risk reduction was 7.4% (-5.2 to 18.6) in favour of clopidogrel, consistent with the observed benefit in the rest of the CAPRIE cohort.

The Antiplatelet Trialists' Collaboration provides strong evidence that long-term use of antiplatelet drugs results in a relative-risk reduction in ischaemic stroke, myocardial infarction, or vascular death, which is consistent across these three clinical subgroups.³ Given this finding and the additional analysis, we judge that the weak evidence of heterogeneity does not invalidate the underlying concept in CAPRIE.

The observed 3-year event rates in the aspirin group for the stroke and peripheral arterial disease subgroups were close to those postulated at the start but were lower in the myocardial infarction subgroup (13 vs 25%). The reasons for this are not clear. It is possible that patient selection was influenced by competing trials in acute myocardial infarction or by investigators keeping those patients with larger infarcts out of this trial in order to give open-label aspirin or anticoagulants. The lower rate may also be due to recent improvements in acute management of patients.

Bias resulting from study execution is unlikely since the blinding was well maintained, the numbers of patients lost to follow-up and treatment code breaks at the clinical centres were small, and the rate of early permanent discontinuation of study drug was lower than reported in similar studies. The central validation of all reported outcome events provided a consistent assessment and should enhance the credibility of the efficacy findings.

Bleeding is a complication of antiplatelet treatment.⁴ Reported severe bleeding was more common with aspirin, with the difference in severe gastrointestinal bleeding being statistically significant. Non-fatal primary intracranial haemorrhage and haemorrhagic deaths were predefined outcome events that could possibly be caused by study drug. These were less frequent in the clopidogrel group (0.39%) than in the aspirin group (0.53%).

Clopidogrel is a thienopyridine derivative, as is ticlopidine. Ticlopidine is known to cause neutropenia (neutrophils less than $1.2 \times 10^9/L$) for which the reported rate of occurrence is about 2.4% and severe neutropenia (less than $0.45 \times 10^9/L$) for which the reported frequency is 0.8%.⁵ In CAPRIE, there was no excess neutropenia in the clopidogrel group. The observed frequency of neutropenia was 0.10% with clopidogrel and 0.17% with aspirin; for severe neutropenia, the corresponding rates were 0.05% and 0.04%. The proportions of patients with severe rash and diarrhoea while on clopidogrel were less than those reported with ticlopidine but twice as high as with aspirin. Although these latter two differences between clopidogrel and aspirin are statistically significant, the absolute difference of about 0.1% is unlikely to be clinically important, and is balanced by the extent of upper gastrointestinal discomfort with aspirin.

Clopidogrel provides an additional 8.7% relative-risk reduction over and above the 25% reduction accepted to be provided by aspirin. Thus, in a patient population similar to that in CAPRIE, aspirin would be expected to prevent about 19 major clinical events versus 24 with clopidogrel, for each 1000 patients treated for 1 year. The efficacy results from CAPRIE are consistent with the previous findings with ticlopidine and indicate that thienopyridines have a greater benefit than aspirin in

patients with atherothrombotic disease, confirming the importance of the P₂Y₁ pathway, compared with the thromboxane pathway in this disease. This benefit was achieved with no evidence of excess neutropenia, a risk of clinically relevant bleeding less than that with 325 mg aspirin per day, and no other toxicity of concern.

Clopidogrel is at least as safe as medium-dose aspirin and is safer than ticlopidine. Given this favourable efficacy/safety ratio, clopidogrel is an effective new antiplatelet agent for use in atherothrombotic disease.

CAPRIE Study Organisation

Steering Committee: M Gent (Chairman), D Beaumont, J Blanchard, M-G Bousser, J Coffman, J D Easton, J R Hampton, L A Harker, L Janzon, J J E Kusmirek, E Panak, R S Roberts, J S Shannon, J Sicurella, G Tognoni, E J Topol, M Verstraete, C Warlow.

Central Validation Committee: M Verstraete (Chairman), J D Easton (V-Chairman), M-G Bousser, J A Cairns, J H Chesebro, J R Hampton, G von der Lippe, R W Ross Russell, P A Wolf.

External Safety and Efficacy Monitoring Committee: J-P Boissel (Chairman), L Friedman, V Fuster, M G Harrison, S Pocock, B B Weksler.

Hamilton Civic Hospitals Research Centre/McMaster University (Canada):

Coordinating and Methods Centre: M Gent, G Foster, G Lewis, T Lychak, H L Nelson, R S Roberts, J Sicurella.

Secretariat for the Central Validation Committee: J Sicurella, C Stewart, B Szechtman.

Canadian Regional Data Collection Centre (RDCC): S Chrolavicius, I Copland, B Jedrzejewski, F McCreddie, L Wilkinson, S Vondervechtn.

Independent Statistical Centre (Lyon, France): J-P Boissel, F Boutitie.

Sanofi Winthrop:

Medical Coordinators: D Beaumont, G Perdriset, I Thizon-de Gaulle, J Hock.

Operational Group and RDCCs: M O Besnier, A Boddy, D Brooker, G Derzko, A Jones, C Metzinger, J Novack, S Pratt, D Roomer, J P Schulhof, E Vallee, D Valtier.

National Medical Monitors: E Bastida, L Coy, R Creek, G Destelle, T Döberl, N de la Forest-Divonne, V Gallo, A Garcia, B Geudelin, F Hundt, R Hylkema, P Vanhove.

Regional Monitors: N Amalfitano, K Cabala, J Caniglia, I Duval, L Forgie, A C Neiss, T Wesseling.

Collaborating Clinical Centres listed by country in order of number of patients enrolled.

USA (4323): Dartmouth-Hitchcock Medical Center, Lebanon (J F Plehn, S J Kennedy, R M Zwolak, A Reeves, M D McDaniel, G J MacDonald, C Murphy, P S Howes, L K Cornell, M L Hynes: 254); University of California, San Diego (C M Jackson, P D Lyden, J F Rothrock, R J Hye, H C Dittich, N M Kelly, C M Kerridge: 148); North Country Neurology Associates, Oceanside (T Chippendale, M Lobatz, E Diamond, J Schim, M Sadoff: 124); St John's Mercy Medical Center, St Louis (W Logan, A Auer, W Hamilton, R Frere, S Schroer, M Wilcox, C Naeger: 122); Virginia Commonwealth University, Richmond (J W Harbison, R Makhoul, J R Taylor, W L Felton III, H M Lee, K Massey-Makhoul: 116); Watson Clinic, Lakeland (K F Browne, G S Tyson, E Pineiro, A S Brenner, R A Ford, P J Reddy, P Owens: 108); St Joseph Mercy Hospital, Pontiac (J Heinsimer, K Richter, K Markowski, T Lentini, L Howell: 107); NISUS Research, Inc., Petoskey (H T Colfer, D J Rynbrandt, C D Wendt, M Wilmot, B Stone: 95); Marshall University, Huntington (R Touchon, D Briley, L Adkins, K Roe, C Harless: 92); Spokane Heart Research Foundation (M A DeWood, J A Skidmore, J M Randall: 92); Minneapolis Veterans Affairs Medical Center (J Davenport, C Farmer, S Hanson: 87); Lovelace Health Systems, Albuquerque (L C Kuo, P Brown, J DesJardins, N Halpern, W Talbot: 83); St Elizabeth Medical Center, Boston (R Schainfeld, K Rosenfield, J M Isber, E Grall: 83); Florida Heart Group, P A, Orlando (S Lanza, P A Walker, R J Ivanhoe, M R Milunski: 82); Christ Hospital, Cincinnati (D J Kereiakes, C W Abbottsmith, D A Lausten: 75); University of Illinois, Chicago (C M Helgason, V Glover, T Gnutek: 74); Oregon Sroke Center, Portland (W M Clark, B M Coull, E Harrison: 70); St Paul Ramsey Medical Center (J T Suh, J W McBride, B Foster K Vitrum, N Y Lauer: 69); Palo Alto (B T Adornato, M K Adornato: 66); University of Southern California, Los Angeles (M Fisher, S F Ameriso, A Scicli: 65); University of Michigan V A M C, Ann Arbor (M R Starling, J A Petruska, W H Devlin: 61); Lovelace Health Systems, Albuquerque

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(C C Suter, J Tucci, S H Stewart: 59); Palm Beach Neurological Group, West Palm Beach (C Sadoway, R Stone, J L Herman: 59); Texas Heart Institute, Houston (E K Massin, H V Andrus, M Harlan: 58); University of New Mexico School of Medicine, Albuquerque (J Abrams, C Timm, G Rosenberg: 58); University of Colorado Health Sciences Center, Denver (W R Hiatt, J G Regensteiner, T Bauer: 56); Barrow Neurological Institute, Phoenix (J L Frey, C Darbonne, L Marlor: 55); University of Nebraska Medical Center, Omaha (W D Haire, L C Stephens, G D Korulak: 54); Chalmers Medical Center (B Iteld, A VanderStappen, V Neuman: 52); Baylor College of Medicine, Houston (N Kleinman, L Bushman, A Fischer: 52); Oregon Stroke Center, Portland (W M Clark, E Harrison, H Moon: 50); University of Minnesota, Minneapolis (A C Klassen, M E S Berman: 50); Northwestern University, Chicago (R Sufit, J Biller: 49); Cleveland Clinic Foundation (J W Olin, C A Pirzada: 49); Buffalo V A Medical Center (L A Hershey, K Burch, K Eschberger: 48); Lehigh Valley Hospital, Allentown (J Castaldo, D Jenny, C Wohlberg: 46); Baptist Memorial Hospital, Memphis (K Gaines, C Cape: 44); Columbia Metro West Medical Center, Framingham (S K Gupta, R A Landa, S R Norcross: 43); V A Medical Center, Syracuse (A Culebras, D C Pastor: 43); Jeanes Hospital, Philadelphia (R M Fairman, S Zakulec: 42); Cleveland Clinic Foundation (J M Sutton, T McCullough: 42); University of Arizona College of Medicine, Tucson (P E Fenster, W M Feinberg: 42); GeronTech, Hot Springs (R G Pellegrino, C Jeffers: 42); Louisiana Cardiovascular Research Center, New Orleans (W B Smith, R Vargas, T McCormick: 41); Henry Ford Health Science Center, Detroit (N M Ramadan, S R Levine: 41); University of Minnesota, Minneapolis (A T Hirsch: 41); George Washington University Medical Center, Washington (A G Wasserman, A Nys: 41); Lahey-Hitchcock Medical Center, Burlington (D J Breslin, S B Labib, G Woodhead: 40); Olympia Fields Osteopathic Hospital and Medical Center (T M Matzura, S Dunlap: 40); Cardiovascular Medical Associates, Mineola (M A Goodman, J Cappelli, P Stein: 39); Denver Health Medical Center (K Nadamanee, E Havranek, J Weinberger: 38); Albany Medical College (N S Lava, S Horowitz: 37); Mercy General Hospital, Sacramento (J Byer, D Wentworth: 37); University of Missouri, Columbia (J D Dexter, A Bonnett: 36); Medical College of Virginia Hospitals, Richmond (G W Vetovec, R P O'Brien: 36); Rhode Island Hospital, Brown University, Providence (J D Easton, J L Wilterdink: 34); Southern Illinois University, Springfield (D A Gelber, S Hemmerger: 33); University of Texas Health Science Center at San Antonio (D Sherman, D Rogers: 31); Duke University Medical Center, Durham (M J Alberts, C McCleenny: 31); Presbyterian Hospital, Charlotte (K D Weeks, D Whisnant: 30); Colombia Metro West Medical Center, Framingham (J D Alton, H Doolittle: 29); New York University Medical Center (K A Siller, W K Hass: 29); William Beaumont Hospital, Royal Oak (C Grines, G Timmis: 29); Rush Medical Center Center for Stroke Research, Chicago (P B Gorelick, D Robinson: 28); Emory University, Atlanta (A B Lumsden, J MacDonald: 27); University of Colorado Stroke Project, Denver (R L Hughes, P Noonan: 27); Moss Rehab Hospital, Philadelphia (G Goldberg, R Costello: 27); Creighton Cardiac Center, Omaha (S Mohiuddin, L Stengel: 26); Emory University, Atlanta (M R Frankel, J Braimah: 26); Brigham and Women's Hospital, Boston (M A Creager, P Baum: 23); Stanford University (J P Cooke, A Ma: 23); Boston University School of Medicine (V L Babikian, M A O'Neal: 22); Cooper Hospital University Medical Center, Camden (T Mirsen, C Bruegel: 21); Boston Medical Center (J D Coffman: 20); Methodist Hospital of Indiana, Indianapolis (D C Brindley, M Mick: 20); UCLA, Los Angeles (S G Korenman: 18); Yale University School of Medicine, New Haven (L M Brass: 18); Neurological Associates, Boise (S W Asher: 15); Mount Sinai Medical Center, New York (J L Halperin: 15); Graduate Cardiology Consultants, Inc., Philadelphia (R Schlesinger: 15); Rochester General Hospital (G M Gacioch: 14); University of Oklahoma Health Science Center (J R Couch, Jr: 11); Graduate Hospital, Philadelphia (B E Skolnick: 11); University of Illinois at Chicago (M S Ware: 9); Doctors' Clinic, Vero Beach (J Anderson: 7); University of Pittsburgh (L Knepper: 5); Cardiology Consultants of Philadelphia (M Victor: 4); University of Massachusetts Medical Center, Worcester (S Ball: 4); University of Kentucky Medical Center, Lexington (J C Gurley: 4); Philadelphia Heart Institute (M Jessup: 3); USC School of Medicine, Los Angeles (U Elkayam: 1).

Canada (3402): Kawartha Cardiology Clinic, Peterborough (W G Hughes, J A Fraser, E A Porvin, J McMillan, J Grierson, N Hartwick, S Musclow, A Thompson, J Mewett, R Sivan: 482); Hamilton Civic Hospitals, General Division (A G G Turpie, S Morino, M Siguenza: 141); Sunnybrook Health Science Centre, North York (J A Blakely, S Styling, L Balleza: 135); University of Ottawa Heart Institute (D S Beanlands, L Garrard, K Morgan, T Ruddy: 133); St Boniface Hospital, Winnipeg (A L Morris, B A Anderson, A S Arneja, S A Carter, V Daniels, B McEwen: 127); Centenary Health Centre, Scarborough (A J Ricci, J H Swan, J E Goode, D A Selby, B Bozek: 125); University of Saskatchewan, Saskatoon (A Shuaib, M Yeung, M Press, L L Walston: 121); Vancouver Hospital and Health Science Centre (A Y Fung, H Henning, D C Taylor, H Abbey, C Davies, L Saunders: 119); St Joseph's Hospital, Hamilton (P H Tanser, D Feldman, B Sullivan, M J Sayles, E Kent: 101); McMaster University, Hamilton

(S J Connolly, E Coletta, V Cuthers: 98); Royal Alexandra Hospital, Edmonton (W Hui, P Klink, J Mass, L Kvill: 96); Hôtel-Dieu de Montréal (J Cusson, P Van Pelt, L Marchand, S Roy, J-F Blair: 94); Ottawa General Hospital (J L Wellington, K Rody, S Poloni: 83); Sunnybrook Health Science Centre, Toronto (M G Myers, C D Morgan, P Parsons: 80); Hôpital Saint-Luc, Montréal (R Lecours, J-V Patenaude, C Turcotte: 80); Kingston General Hospital (J R Gutelius, R Patten: 74); Hôpital Notre Dame, Montréal (R-M Gagnon, N Racine, C Roy: 72); Victoria Hospital, London (K Harris, M Lovell: 71); Vancouver Hospital and Health Sciences Centre (P A Teal, J-L Bloomer: 71); St Paul's Hospital, Vancouver (C R Thompson, M Wong, J G Sladen, K MacDonald, D Heinrich: 70); Hôpital de l'Enfant-Jésus, Québec City (G Houde, C Nadeau, P Talbot: 64); Hôpital du Sacré-Coeur de Montréal (A Pagé, A Verdant: 60); Royal Victoria Hospital, Montréal (M Smilovitch, N Racine, O Steinmetz: 60); Hôpital de l'Enfant-Jésus, Québec City (D Simard, C Benguigui, C Ouellet: 53); Hôpital Saint-Luc, Montréal (L-H LeBrun, M P Desrochers: 52); Victoria Hospital, London (K Finnie, S McCreery: 52); London Health Sciences Centre, University Campus (W J Kostuk, P W Pflugfelder, R Oskalan: 50); Apex Clinical Research Inc., Victoria (J F Bonet, K Ilott, J McConnell: 50); Hôpital Saint-Luc, Montréal (M Ruel, L Primeau: 49); Queen Elizabeth II Health Sciences Centre, Halifax (S Phillips, L Coleman-Kamphuis: 49); Montreal General Hospital (J R Leclerc, S Solymoss: 46); Montreal General Hospital (R Côté, F Bourque: 44); Grey Nuns Hospital, Edmonton (T K Lee, L Kvill: 44); Vancouver Hospital and Applied Sciences Centre (V Bernstein, L Doyle: 40); Hôpital Charles LeMoine, Greenfield Park (J R Timothee, R Chebayeb: 40); Toronto East General Hospital (C Lefkowitz, P Hambly: 40); Calgary General Hospital (G M Klein, M Robertson: 38); St Michael's Hospital, Toronto (N Bayer, P Couse: 31); Sunnybrook Health Science Centre, Toronto (J W Norris, M J Medel: 29); Queensway General Hospital, Etobicoke (B Sevirt, J Fitzsimons: 27); Royal Victoria Hospital, Montreal (D Fitchett, A Serpa: 20); Saint John Regional Hospital (D Marr, B Ouellet: 20); Hôpital Charles LeMoine, Greenfield Park (A Bellavance: 18); Memorial University of Newfoundland, St John's (W Pryse-Phillips: 16); Queen's University, Kingston (D C Howse: 14); University of British Columbia, Vancouver (S W Rabkin: 11); The Sir Mortimer B Davis Jewish General Hospital, Montreal (J McCans: 7).

Netherlands (2461): Academic Medical Center and Slotervaart Hospital, Amsterdam (D P M Brandjes, H R Büller, A R A Dykema, J G Kromhout, J A Lawson, R J Peters, J J van der Sande, J Stam, L M Blok, Y Jenner, O Termede: 307); The Wever Hospital, Heerlen (J Lens, E C M Bollen, R J Th J Welten, Ph Termeulen, W P M F Hollanders: 278); Deventer Hospital (D J A Lok, H Groeneveld, L H M Bouwens, F C W Tietge, E C M van der Velden, P W F Bruggink-André de la Porte: 260); Slingeland Hospital, Doetinchem (J G J M van Iersel, J Seegers, A C van Vliet: 243); SMT, Hengelo (P van der Sar, B D Verhoog, S H van der Sar-de Nooijer, I Verhoog-Nijhuis: 175); The Wever and Gregorius Hospital (C L Franke, P J Koehler: 173); Cardiology Centre, Groningen (J van der Meer, J S van Os, M van der Heijden, L M van Wijk: 173); The Wever Hospital, Heerlen (J A Kragten, J de Warrimont-Henquet, R Feld: 109); University Hospital, Rotterdam (H M Van Gemert, D W J Dippel, P J Koudstaal: 103); Sint Lucas Andreas Hospital, Amsterdam (J A L Vanneste, W H J P Linsen, J J M Kruisdijk: 100); Sint Lucas Andreas Hospital, Amsterdam (J Visser, T F Van Gool, J Vooges: 95); Westeinde Hospital, The Hague (A C De Vries, P Klinkert, K A Bartlema: 84); University Hospital, Utrecht (J D Banga, S D J M Niemeijer-Kanters, M G de Groot: 79); St Antonius Hospital, Nieuwegein (F L Moll, R Sybrandy: 72); Catharina Hospital, Eindhoven (J Buth, F P G Schol: 59); University Hospital, Utrecht (R C J M Donders, A Algra: 54); Holy Ziekenhuis, Vlaardingen (G A M Pop, R van der Heijden: 52); Leyenburg Hospital, The Hague (B Knippenberg, J C Sier: 45).

Sweden and Finland (1650): University Hospital, Uppsala (D Berqvist, S Karacagil, I Eriksson, S Bowald, A Holmberg, C Ljungman, B Westman: 239); University of Kuopio (J Sivenius, J Puranen, A Karinen, J Onatsu, T Salmenperä, M Kalinen: 231); Helsinki University Central Hospital (M Kaste, T Tadisumak, L Soenne, M Kallala, M Kotila: 160); Sahlgrenska University Hospital (M Hartford, J Herlitz, B W Karlson, S-O Strömblad: 152); Umeå University Hospital (B-O Olofsson, T Strand, B Kristensen, J Malm: 136); Jyväskylä Central Hospital (J H Melin, M Virtanen, T Olli: 112); Malmö University Hospital (F Lindgärde, H Pessah-Rasmussen, M Rendell, U-B Ericsson: 94); Helsinki University Central Hospital (A Sahlan, H Savolainen, J Rämö, J Lehtonen: 83); University of Oulu (M E Hillbom, M Reunanen, J Turkka: 72); University of Oulu (K Ylönen, T Peltola, T Juvonen: 60); Central Hospital of Kotka (E Koskela, J Erkinheimo: 53); University Hospital, Umeå (K-A Ångquist, B Hedberg, C Arnerlov: 50); Central Hospital of Central Finland, Jyväskylä (A Rissanen, K Muuronen: 48); Jorvi Hospital (U Idänpää-Heikkilä, L Honka: 44); Helsinki University Central Hospital (J Heikkilä, T Tiensuu: 42); University Hospital, Uppsala (J Boberg, A-L Berggren: 41); Keski-Suomen Keskussairaala, Jyväskylä (H Riekkinen, P Kuukasjärvi: 33).

Australia and New Zealand (1537): Sir James Gairdner Hospital, Nedlands (P L Thompson, E T M Yu, J D Shaw, P A Cooke, S P F Gordon, K S H Loh, B McQuillan, M Moshiri: 239); Royal Brisbane Hospital (D B Cross, W S Egerton, P J Walker, C A Codd, D A Kreuter, S Cox, D Naik, D M Cavaye, M C Harel: 224); The Queen Elizabeth Hospital, Woodville (J Horowitz, C Rowe, S Stewart, K Boundy, C F Stringer, J L Anderson, D Coller: 159); Flinders Medical Centre, Bedford Park (P Aylward, C Anderson, R Burns, D Schultz, P Waddy, J Walsh: 140); Royal Prince Alfred Hospital, Camperdown (L Davies, J P Harris, A Wetzlar, A McDougall, K Sieunarine, P Cremer: 123); Austin Hospital, Heidelberg (G A Donnan, A Tonkin, C Levi, J Hanlan, F Ellery: 122); Green Lane Hospital, Auckland (H D White, A W Hamer, V Kapadia, K Ramanathan: 90); Royal Perth Hospital (R R Taylor, G Hankey, M Brooks, T Young, M McInerney: 82); Royal Hobart Hospital (J Sansom, R Thomson, C Spaulding, R Cuthforth, A Thomson: 81); Box Hill Hospital (H H Salem, P Coughlin: 78); St Vincent's Hospital, Darlinghurst (T J Campbell, R S A Lord, D O'Sullivan, C Corrigan, S D'Arcy: 77); Auckland Hospital (N E Anderson, A J Charleston: 47); Royal Melbourne Hospital (S M Davis, R Gerraty: 44); The Prince Charles Hospital, Chermiside (N Bett: 16); Greenslopes Private Hospital (D J Hewson: 15).

UK (1431): St James University Hospital, Leeds (R C Kester, D J A Scott, D C Berridge, P J Kent, C A Thornton, H Sykes, S Bennett: 332); Queen's Medical Centre, Nottingham (D Blakey, W P Brooksby, R T Johnston, M Brack, J R Hampton: 180); Bradford Royal Infirmary (P Vowden: 169); Leeds General Infirmary (M J Gough, R Hooper, M Gough: 135); North Manchester General Hospital (S P Hanley, M MacAskill, J Miles, C Waywell: 115); North Staffordshire Hospital (J C Mucklow, C Davis, P Harper, K Cooke: 100); University Royal Infirmary, Glasgow (G Lowe, B Shaw, J McKillop: 72); St George's Hospital, London (J A Dormandy, H Chaudhry, J Evans: 70); St James University Hospital, Leeds (J M Bamford, S Blundell: 53); Central Sheffield University Hospitals (G Venables, C Doyle: 40); Queen Elizabeth Hospital, Birmingham (C P Shearman, A Crow: 39); Western General Hospital, Edinburgh (M Dennis, P Sandercock: 38); St George's Hospital, London (M M Brown, J Rogers: 35); York District General Hospital (R M Boyle, B S Wiseman: 31); Walton Centre for Neurology and Neurosurgery, Liverpool (P R D Humphrey: 11); Academic Unit of Medicine, Leeds (C R M Prentice: 11).

Switzerland (1256): Hospital Civico, Lugano (T Moccetti, E Pasotti, F Sessa, A Bertolini, A Rossi, A Del Bufalo, R Malacrida, D Moccetti, G Besomi: 229); Inselspital, Bern (H P Mattle, E Eicher Vella, D Maurer, F Rihs: 111); University Hospital, Zürich (U Hoffmann, A Bollinger, U K Franzeck: 76); Inselspital, Bern (F Mahler, D Do, I Baumgartner: 73); Kantonsspital St Gallen (B Weder, L Bönig, H-P Ludin: 68); Centre Hospitalier Universitaire Vaudois, Lausanne (J Bogousslavsky, M Maeder-Ingvarg, F Regli: 65); Centre Hospitalier Universitaire Vaudois, Lausanne (L Kappenberger, M Depairon, G Bizzini: 65); Ospedale Italiano di Lugano, Viganello (C Beretta-Piccoli, F Elshater-Zanetti, C Guffi: 65); Triemli Hospital, Zürich (G Bertel, T Desèd, W Gmuer: 60); University Hospital of Geneva (H Bounameaux, J Wicky, S Desmarais: 57); Hôpital de Sion (P Vogt, D Fellay: 52); Kantonsspital Glarus (K Rhyner, W Wojtyna, T Bonetti, J Brunner: 52); University Hospital, Basel (K A Jäger, I von Planta: 50); Ospedale della Beata Vergine, Mendrisio (G Nosedà, A Pugliesi, L Pons-Giudici: 45); University Hospital, Bern (B Meier, D Evéquoz: 42); Kantonales Spital Walenstadt (D Schmidt, H S Keel, D Heinrich: 42); University Hospital, Zürich (F Follath, H P Brunner: 34); Spital Limmattal, Schlieren (B Caduff, M Wirth: 28); Kardiologie Kantonsspital Aarau (A Vuilliamenot: 21); Centre Hospitalier Universitaire Vaudois, Lausanne (M Savcic: 19); Zürcher Höhenklinik Wald, Faltigberg (U Hürlimann: 1); Bezirksspital, Herzogenbuchsee (E Bosshard: 1).

Germany and Austria (959): University of Heidelberg (W Hacke, T Brandt, S Wildermuth, P Ringleb: 105); University of Minden (O Busse, V Straeten, K Zeuner, St Vielhaber: 92); University of Mainz (B Tetenborn, G Krämer, A Allardt, E Schmitt-Henco: 90); University of Essen (H-C Diener, V Schrader, J Nebe: 65); Medical University of Graz (E Pilger, A Doder, B Gürtl: 64); University of Karlsruhe (C Diehm, M Gomer, T Jansen: 61); University of Lübeck (D Kömpf, M Kaps, M Vidal-Langwasser: 56); University of Heidelberg (M Hennerici, M Daffertshofer, U Schmink: 53); University of Ulm (H H Osterhues, A Fischer: 48); University of Mainz (H-J Rupprecht, U Borkowski: 41); University of Essen (G Rudofsky, A Rescher: 41); University of Homburg Saar (H Schwerdt, B Hammer: 40); University of Giessen (R Voss, M Grebe: 40); University of Engelskirchen (H Rieger, R Grobe: 37); University München (TU) (W Theiss, F Schaub: 37); University of München (F-J Neumann, L Lutlisky: 27); Landeskrankenhaus, Innsbruck (F T Aichner, C Schmidauer: 25); University of Saarland (K Erdlenbruch, B S Mörsdorf: 23); University of Giessen (C R Hornig: 14).

France (916): Department of Neurology, Besancon (T Moulin, D Chavot, M-H Snidaro: 80); Hôpital Bretonneau, Tours (A Aurret: 78); CHU Lille (C Caduc, D Leys, H Henon: 63); Centre Hospitalier de Meaux

(F Chedru, A Ameri, J-F Maquie: 56); Hôpital de Freyming-Merlebach (P Dambrine, A Gabriel, J-F Maquie: 55); Hôpital de Longjumeau (X Tran-Thanh, C Jouanneau, J Durup: 55); CHU Gui de Chauliac, Montpellier (M Pages, J M Blard: 50); Hôpital General, Dijon (M Giroud, M Menassa: 49); Hôpital Sainte-Anne, Paris (M Zuber, J L Mas: 42); Hôpital La Tronche, Grenoble (M Hommel, G Besson: 36); St Joseph Hospital, Paris (C Laurian, J-F Mathieu: 36); CHU de Rangueil, Toulouse (G Geraud, V Larrieu: 36); Hôpital Cochin, Paris (K Ben-Hamda, R Furney: 35); Hôpital Purpan, Toulouse (B Guiraud-Chaumeil, F Chollet: 34); CHI de Poissy (M Pathé, D Zannier-Marzari: 34); Saint Antoine Hospital, Paris (H Chabriet, P Amarengo: 29); CHRU Pontchaillou, Rennes (J-F Pinel: 28); Hôpital Louis Pradel, Lyon (J Beaune, J-B Pichard: 28); Clinique du Parc Rambot, Aix-en-Provence (A Medvedowsky: 28); University Hospital, Dijon (F Becker, B Terriat: 27); Hôpital Lariboisière, Paris (F Woimant: 19); Hôpital Saint Louis, Paris (G Cathelineau: 18).

Spain (421): Hospital General La Paz, Madrid (I Martin Jadraque, J L López Sendon, I Gonzales Maqueda, I Roldan Rabadan: 100); Hospital Universitario Virgen, Macarena (J M Cruz Fernández, V López Garcia: 91); Hospital Clinico San Cecilio, Sevilla (E Ros Die, J Gonzales Rios, O Del Foco: 64); Hospital Clinico, Barcelona (A Chamorro, M Alday: 44); Hospital General de Alicante (J Matias-Guiu, F Gracia: 39); Hospital Clinico, Barcelona (J L Pomar Moya-Prats, C A Mestres: 33); Hospital General La Paz, Madrid (J A Jiménez Cossio, L Riera de Cubas: 28); Hospital General La Paz, Madrid (P Barreiro Tella, E Diez Tejedor: 22).

Portugal (355): Hospitais da Universidade de Coimbra (L Cunha, A F Gonçalves, M A Ferro, V Barbosa, D Santiago: 151); Hospital St Maria, Lisbon (J M Ferro, T P Melo, V Oliveira, A N Pinto: 95); UTIC - Arsénio Cordeiro Hospital Santa Maria, Lisbon (A L Bordalo-Sá, D Ferreira, J L Tuna: 49); Coimbra University Hospital (L Providência, J Morais: 49); Hospital Geral Santo António, Porto (A Pimenta: 11).

Belgium (291): U Z Gasthuisberg, Leuven (F Van de Werf, A Luyten, C Luys: 51); Erasme University Hospital, Bruxelles (S A Blecic, N G Van Blercom, J G Hildebrand: 50); CHU de Liège (B Sadzot, G Franck: 40); Cliniques Universitaires Saint Luc, Bruxelles (C Brohet, D Huyberechts: 37); CHR de la Citadelle, Liège (M Zicot, J Petermans: 33); University Hospital, Gent (D A Duprez, D L Clement: 32); U Z Gasthuisberg, Leuven (R Verhaeghe, K Peeterlinck: 25); University Hospital, Gent (J De Reuck: 14); CHU Saint-Pierre, Bruxelles (Th Bosschaerts: 8); Erasme University Hospital, Bruxelles (J C Wautrecht: 1).

Italy (183): University Hospital St Orsola, Bologna (S Coccheri, G Fortunato: 35); Biomedical Science Institute, Milano (M Catalano, A Libretti: 31); University of L'Aquila (A Carolei, S Mearrelli: 31); Università di Perugia (P Gresle, L Selli: 27); Università di Perugia (G G Nenci, M Morini: 20); University of Milan (M Cortellaro: 19); Istituto Scientifico H San Raffaele (S L Chierchia: 14); University degli Studi, Siena (G Luca Messa: 6).

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West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials

West of Scotland Coronary Prevention Group*

Summary

Background We assessed the potential benefit of treatment for low-risk and high-risk groups in the West of Scotland Coronary Prevention Study (WOSCOPS) population, and compared the benefits of primary and secondary prevention of coronary heart disease (CHD) by lipid lowering with the benefits of blood pressure reduction in the primary prevention of stroke.

Methods We did a subgroup analysis of placebo-treated men in the WOSCOPS population by age, vascular disease at trial entry, and other established risk factors. We also compared WOSCOPS findings with those of the Scandinavian Simvastatin Survival Study (4S) and the Medical Research Council (MRC) trial of treatment for mild to moderate hypertension in middle-aged men. The WOSCOPS population comprised 6595 men aged 45-64 years with no history of myocardial infarction (MI) and plasma total cholesterol concentrations of 6.5-8.0 mmol/L at initial screening. Participants were randomly allocated pravastatin (40 mg daily) or placebo, and followed up for an average of 4.9 years.

Findings Coronary event rates at 5 years in the WOSCOPS placebo group were higher than 10% (the recommended treatment threshold) in men with pre-existing vascular disease and in those 55 years or older without symptoms or signs of CHD but with at least one other risk factor. Event rates were low in men with hypercholesterolaemia but no other risk factor: 3.5% (95% CI 1.3-5.7) for men aged 45-54 years and 5.3% (2.7-8.0) for men aged 55-64 years. Three times more men had to be treated for 5 years to prevent one endpoint in WOSCOPS than in 4S. By contrast, two to four times fewer men with hyperlipidaemia were treated to save one coronary event in WOSCOPS than hypertensives to save one stroke in the MRC trial. These differences persisted after adjustment for the low-risk status of many of the patients with hypertension who took part in the MRC trial.

*Writing committee and participants listed at end of article

Correspondence to: Dr Christopher Isles, Department of Medicine, Dumfries and Galloway Royal Infirmary, Dumfries DG1 4AP, UK

Interpretation There were a substantial number of men whose risk of a coronary event was more than 10% at 5 years in the WOSCOPS cohort. The absolute benefit of pravastatin treatment of hyperlipidaemia is less in the primary prevention of CHD than in secondary prevention, but is similar to that for primary prevention of stroke by treatment of mild to moderate hypertension in middle-aged men.

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Introduction

After publication of the West of Scotland Coronary Prevention Study (WOSCOPS)¹ of pravastatin in men with hypercholesterolaemia we decided to re-examine the role of lipid-lowering drugs in the prevention of coronary heart disease (CHD). WOSCOPS showed that in men aged 45-64 years who had raised serum cholesterol (6.5-8.0 mmol/L), but no previous myocardial infarction (MI), pravastatin treatment reduced the relative risk of non-fatal MI or death definitely attributable to CHD by 31%, that of death definitely or probably related to CHD by 33%, that of death from all cardiovascular causes by 32%, and that of death from any cause by 22%. The absolute risks of these endpoints at 5 years were reduced by 2.4%, 0.6%, 0.7%, and 0.9%, respectively. The proportionate benefit from pravastatin was similar in all subgroups of patients.¹

The findings of WOSCOPS could, in theory, be applied to a substantial proportion of many populations² and would lead to widespread drug treatment. However, this approach may not be desirable or economically feasible because of the constraints on modern health-care systems. Our examination of the issue of the benefit of treatment starts from the position that there is a wide range of absolute risk for CHD morbidity and mortality in our cohort; with a uniform proportionate risk reduction, there should be a corresponding variation in the absolute benefit of treatment.

As a precursor to a detailed examination of cost benefit, we did a subgroup analysis of the WOSCOPS population to identify the characteristics of the men at the highest absolute risk of CHD. We also compared the effect of cholesterol lowering on primary prevention of CHD (as